

Pathogenesis of UTI in Women with Diabetes Mellitus

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Urinary tract infections in Diabetes mellitus

- **Prevalence is increased in women compared to non-diabetics of the same gender**
- **Prevalence is not increased in male diabetics**
- **Many infections are asymptomatic (ASB)**
- **Most infections are complicated (50% ACB)**
- **Increased in pregnancy and related to prematurity and new-born mortality**
- **Most important cause of bacteremia in diabetics**

(Geerlings et al. Diabetes Care 2000;23(6):744-49)

Concepts of increased rate of infection in diabetics

- Patients with diabetes mellitus have organ dysfunction (Neuropathy, Bladder dysfunction)
- Patients with diabetes mellitus are immunocompromised
- Bacteria grow better in glucose
- Micro-organisms in diabetics express different virulence factors
- Bacteria adhere better in patient with diabetes mellitus

Urinary tract infections in Diabetes mellitus

University Medical Center Utrecht Research project

- **Is the incidence of ASB in women increased?**
- **Is there a difference between type-1/2 patients?**
- **With which risk factors is the increased incidence correlated?**
- **What are the type of bacteria causing ASB/UTI and what virulence factors do they express?**
- **What are the consequences of asymptomatic bacteriuria**
- **What is the pathogenesis of ASB in diabetics**
- **Started in 1996 with a grant from DF Netherlands**

Objectives of the clinical part

To determine in a multi-center study:

- The prevalence of asymptomatic bacteriuria (ASB) in women with DM
- The risk factors for ASB in women with DM type 1 and DM type 2
- Consequences of ASB

Results (1) - Prevalence

| | ASB+ | ASB- | Control ASB + n= 153 |
|-----------------|-----------|-----------|----------------------------|
| All n=636 | 163 (26%) | 473 (74%) | 9 (6%) |
| Type-1 N=258 | 53 (21%) | 205 (79%) | |
| Type-2 N=378 | 110 (29%) | 268 (71%) | |

Risk factors for all women with DM

| | ASB- | ASB+ | p-value | or |
|----------------------|-------------|-------------|----------------|-----------|
| number | 473 (74%) | 163 (26%) | | |
| retinopathy | 119 (25%) | 57 (35%) | 0.01 | 1.2 |
| albuminuria | 18 (6%) | 18 (16%) | 0.002 | 3.1 |
| BMI | 27.8 | 26.8 | 0.004 | 1.0 |
| UTI last year | 83 (18%) | 43 (26%) | 0.009 | 1.9 |
| duration DM | 13.1 | 14.9 | 0.07 | |
| HbA1c | 8.5 | 8.6 | 0.5 | |

Risk factors DM type 1

| | ASB- | ASB+ | p-value | or |
|------------------------------|-----------|----------|---------|-----|
| number | 205 (79%) | 53 (21%) | | |
| Neuropathy | 44 (23%) | 20 (40%) | 0.03 | 2.2 |
| Macroalbumi nuria | 8 (5%) | 7 (16%) | 0.02 | 3.6 |
| Duration DM | 17.9 | 22.4 | 0.02 | |
| HbA1c | 8.5 | 8.8 | 0.3 | |

Yellow= multivariate analysis

Risk factors DM type 2;n= 378

| | ASB- | ASB+ | p-value | or |
|----------------------|-----------|-----------|---------|-----|
| number | 268 (71%) | 110 (29%) | | |
| Age | 58.0 | 63.0 | <0.001 | |
| albuminuria | 10 (6%) | 11 (15%) | 0.03 | 2.9 |
| BMI | 29.9 | 28.3 | 0.04 | 1.0 |
| UTI last year | 48 (18%) | 30 (27%) | 0.02 | 1.9 |
| Duration DM | 9.3 | 11.3 | 0.05 | |
| HbA1c | 8.6 | 8.5 | 0.9 | |

Yellow=multivariate analysis

Conclusion (1)

Prevalence of ASB is increased (26%-6%; $p < 0.001$)

Risk factors in type-1 are peripheral neuropathy and macroalbuminuria

Risk factor in type-2 is age

No effect of regulation, a post-voiding bladder residue, various contraceptive methods, estrogen treatment, sexual intercourse, cardiovascular dysfunction

**ASB is suggested in some studies non-
diabetics to lead to:**

-recurrent UTI

-hypertension

-renal impairment

-increased mortality

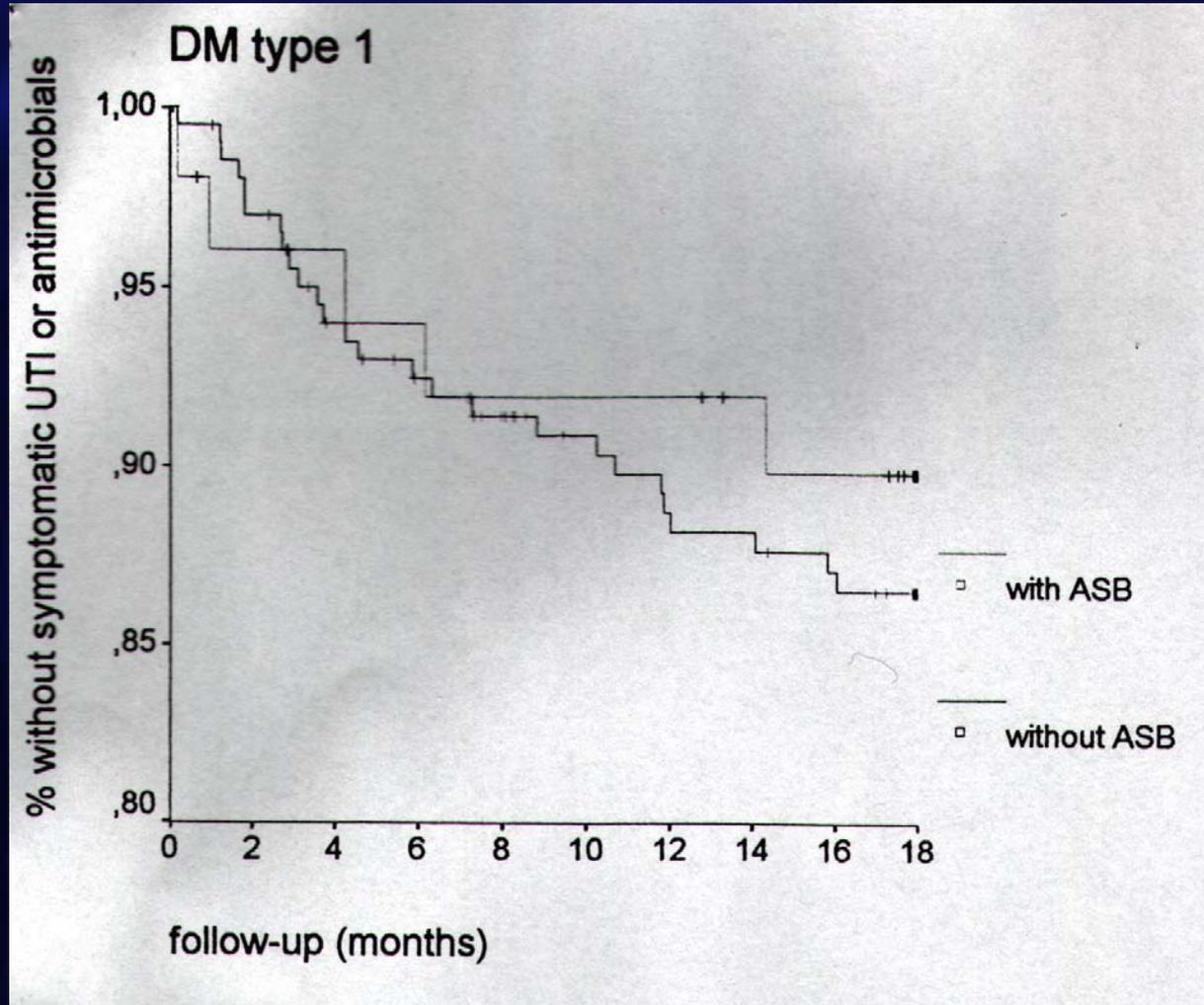
What are the consequences of ASB (to treat or not to treat that's the question)

- **Development of symptomatic UTI**
- **Effect on renal function**

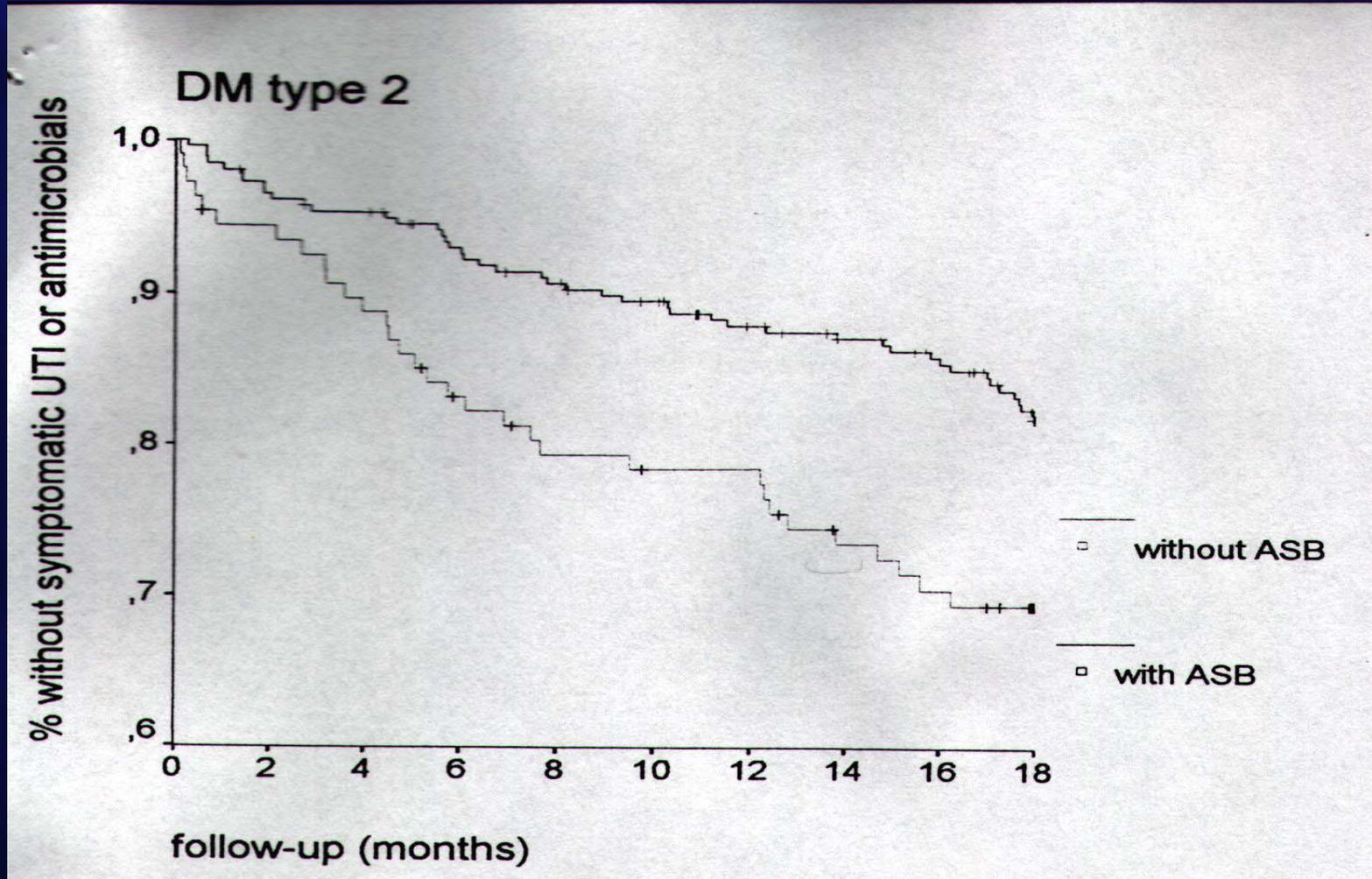
Follow up characteristics of all women with DM

| N=589 | ASB- | ASB+ | P |
|---|--------------------|--------------------|------------|
| | N=441 (75%) | N=148 (25%) | |
| UTI | 75 (17%) | 40 (27%) | .02 |
| Antimicrobial Therapy UTI | 62 (14%) | 34 (23%) | .01 |
| Increase In creatinine clearance | 4.4% | 5.6% | .26 |

Consequences of ASB in type-1 DM



Consequences of ASB in type-2 DM



Follow up characteristics of all women with DM type-1

| N=241 | ASB – N=192 (80%) | ASB+ N=49 (20%) | P-value |
|----------------------------------|------------------------------|----------------------------|----------------|
| Symptomatic Uti | 28 (15%) | 6 (12%) | .8 |
| Antimicrobial Therapy UTI | 25 (13%) | 5 (12%) | .7 |
| Increase In Creatinine | 1.5% | 4.6% | .2 |
| Albuminuria Increase | -19% | -25% | .9 |

Follow up characteristics of all women with DM type-2

| N=348 | ASB – N=249 (72%) | ASB+ N=99 (28%) | P-value |
|----------------------------------|------------------------------|----------------------------|----------------|
| Symptomatic Uti | 47 (19%) | 34 (34%) | .006 |
| Antimicrobial Therapy UTI | 37 (15%) | 29 (29%) | .003 |
| Increase In Creatinine | 6.1% | 6.6% | .9 |
| Albuminuria Increase | -28% | -43% | .4 |

Conclusion (2)

27% of women with ASB develop a symptomatic infection

ASB at baseline increases the risk for a symptomatic UTI (17 vs. 27% p=0.02)

More antibiotics are prescribed (p=0.01)

Women with type-1 DM have a relative faster decline in renal function (4.6% vs. 1.5%)

Geerlings et al Arch Intern Med, 2001; 161 (11): 1421-7

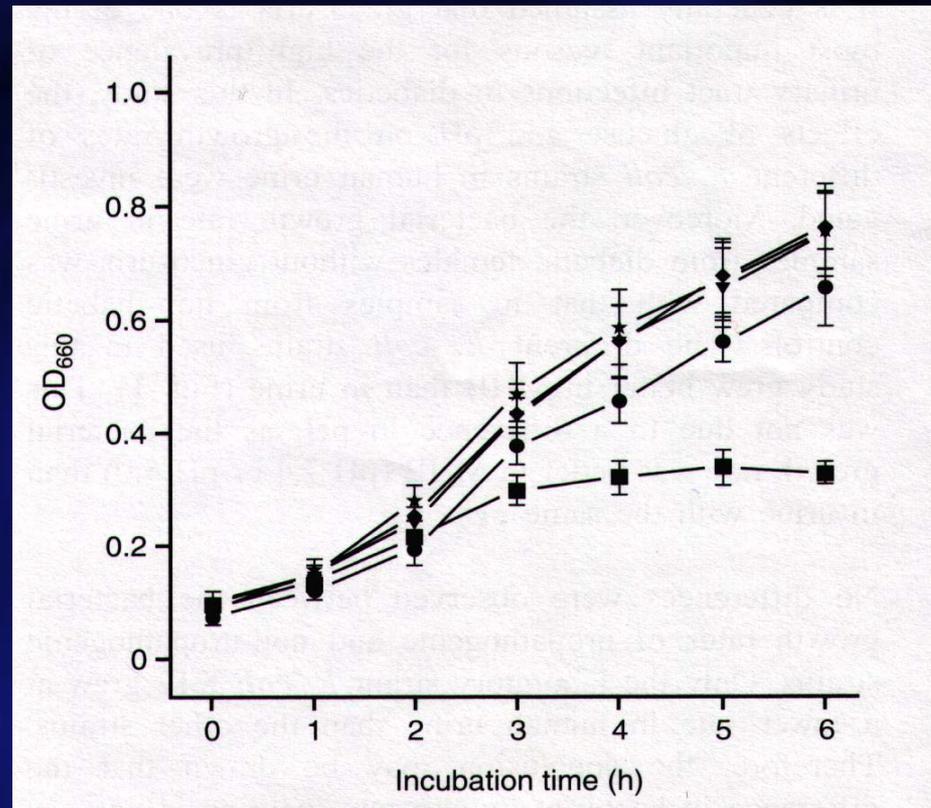
Pathogenesis of increased rate of bacteriuria in women with diabetes mellitus

- **Different micro-organisms are seen in diabetics**
- **Micro-organisms in diabetics express different virulence factors**
- **Bacteria grow better in glucose**
- **Patients with diabetes mellitus are immunocompromised**
- **Adherence of microorganisms has changed**

Concepts of increased rate of urinary tract infections in diabetics

- Bacteria grow better in glucose

Effect of glucose on growth of *E.coli* in urine



Concepts of increased rate of infection in diabetics

- Bacteria grow better in glucose
- Different micro-organisms are seen in diabetics

Bacteria found in diabetic women with ASB

636 women: 163 ASB (26%)

- ***E.coli* 42% compared to 78% in control group**
- **Other Enterobacteriaceae 30%**
- **Hemolytic streptococcus group B 10%**
- ***Enterococcus spp***
- ***S.aureus***

Correlation of bacterial factors and patients' characteristics

E.coli

| Bacterial factor | Abnormal UT | | Medical Illness | | One or more | |
|------------------|-------------|----|-----------------|----|-------------|-----|
| | Y | No | Y | No | Y | No |
| P fimbriae (%) | 45 | 82 | 42 | 76 | 52 | 100 |
| Type 1 | 81 | 96 | 83 | 91 | 85 | 100 |
| Hemolysin | 46 | 44 | 46 | 44 | 44 | 50 |

Virulence factors in 111 *E.coli* isolated from diabetic women

| | | |
|---------------|----|-----|
| type 1 | 96 | 87% |
| MSHA | 65 | 59% |
| subunit-A | 22 | 20% |
| G-adhesin-I | 0 | 0% |
| G-adhesin-II | 5 | 5% |
| G-adhesin-III | 16 | 15% |
| MRHA | 21 | 19% |
| sfa | 33 | 30% |
| afa | 6 | 5% |
| CNF | 21 | 19% |
| aerobactin | 35 | 32% |
| hemolysis | 36 | 33% |
| O-UTI | 21 | 19% |

Correlation of virulence factors with clinical consequences (increase in creatinine)

| VF | N | Creatinin increase without VF | Creatinin increase with VF | P-VALUE |
|-------------|------------|-------------------------------|----------------------------|------------|
| Type 1 | 90% | 6.3% | 6% | .97 |
| MSHA | 60% | 2.1% | 8.1% | .08 |
| Pap A | 24% | 5.9% | 4.7% | .82 |
| MRHA | 22% | 4.9% | 8.7% | .48 |
| SFA | 35% | 4.2% | 10.4% | .18 |
| AFA | 4% | 6.4% | 4.4% | .87 |
| Aerobactin | 32% | 6.5% | 3.9% | .56 |
| CNF | 21% | 3.9% | 12.6% | .11 |
| Hemolysis | 33% | 4.1% | 8.4% | .34 |

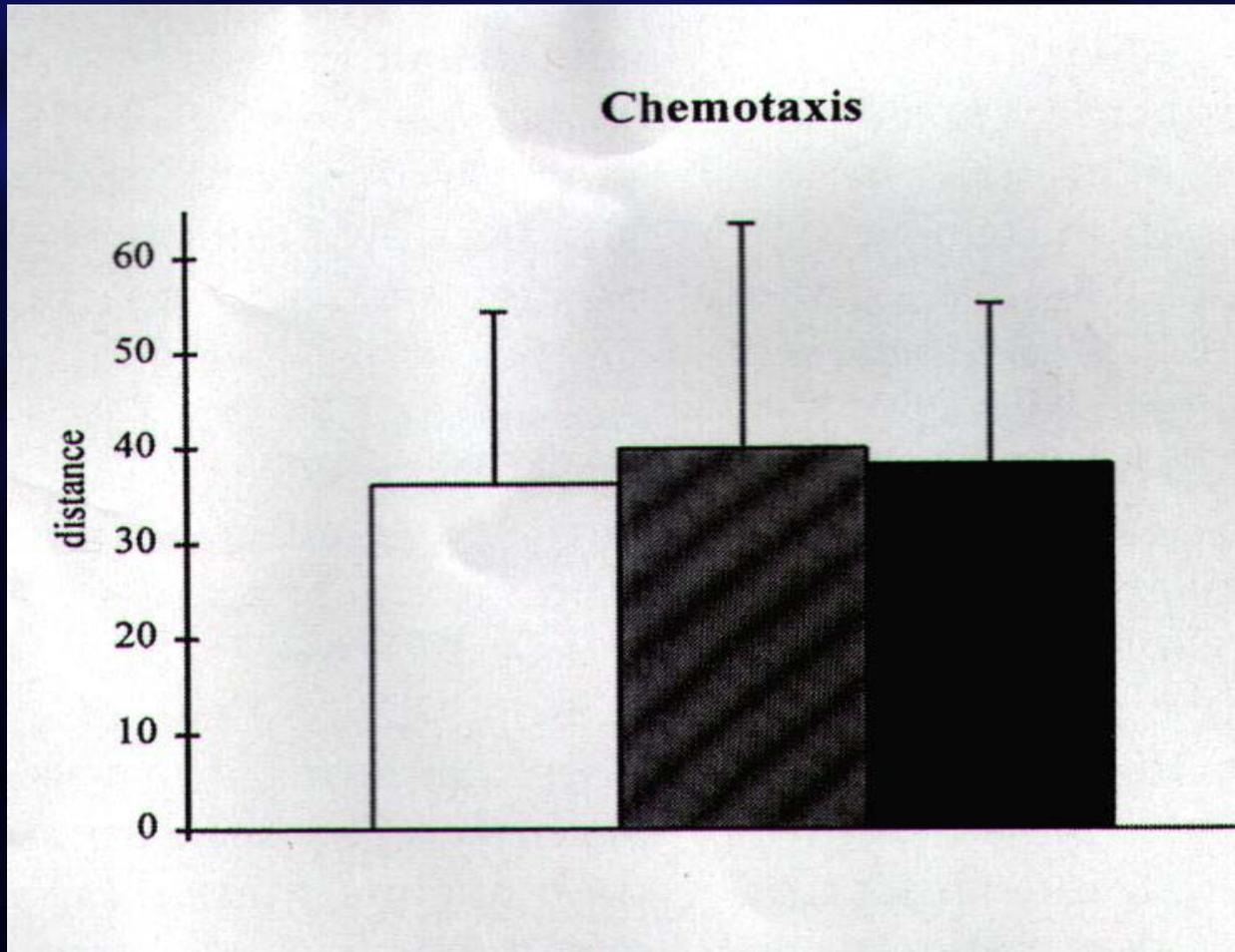
Correlation of virulence factors with clinical consequences (symptoms)

| VF present | N | No symptomatic UTI | Symptomatic UTI | P-VALUE |
|-------------------|------------|--------------------|-----------------|------------|
| Type 1 | 90% | 89% | 16% | .16 |
| MSHA | 60% | 55% | 75% | .15 |
| Pap A | 24% | 30% | 6% | .05 |
| MRHA | 22% | 26% | 6% | .09 |
| SFA | 35% | 40% | 25% | .28 |
| AFA | 4% | 4% | - | .42 |
| Aerobactin | 32% | 42% | 13% | .03 |
| CNF | 21% | 25% | 6% | .11 |
| Hemolysis | 33% | 30% | 50% | .18 |

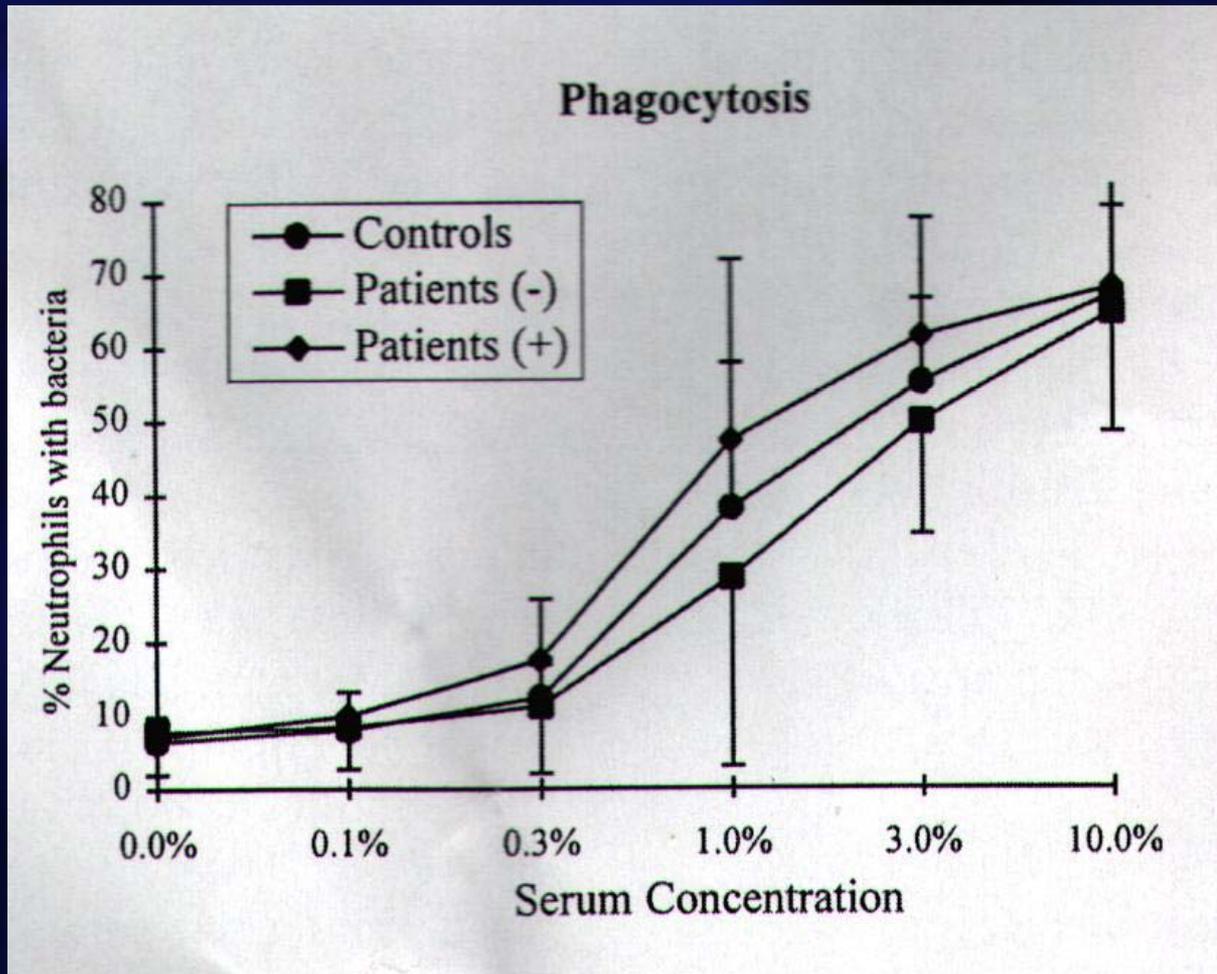
Concepts of increased rate of infection in diabetics

- Bacteria grow better in glucose
- Different micro-organisms are seen in diabetics
- Patients with diabetes mellitus are immunocompromised -PMN function

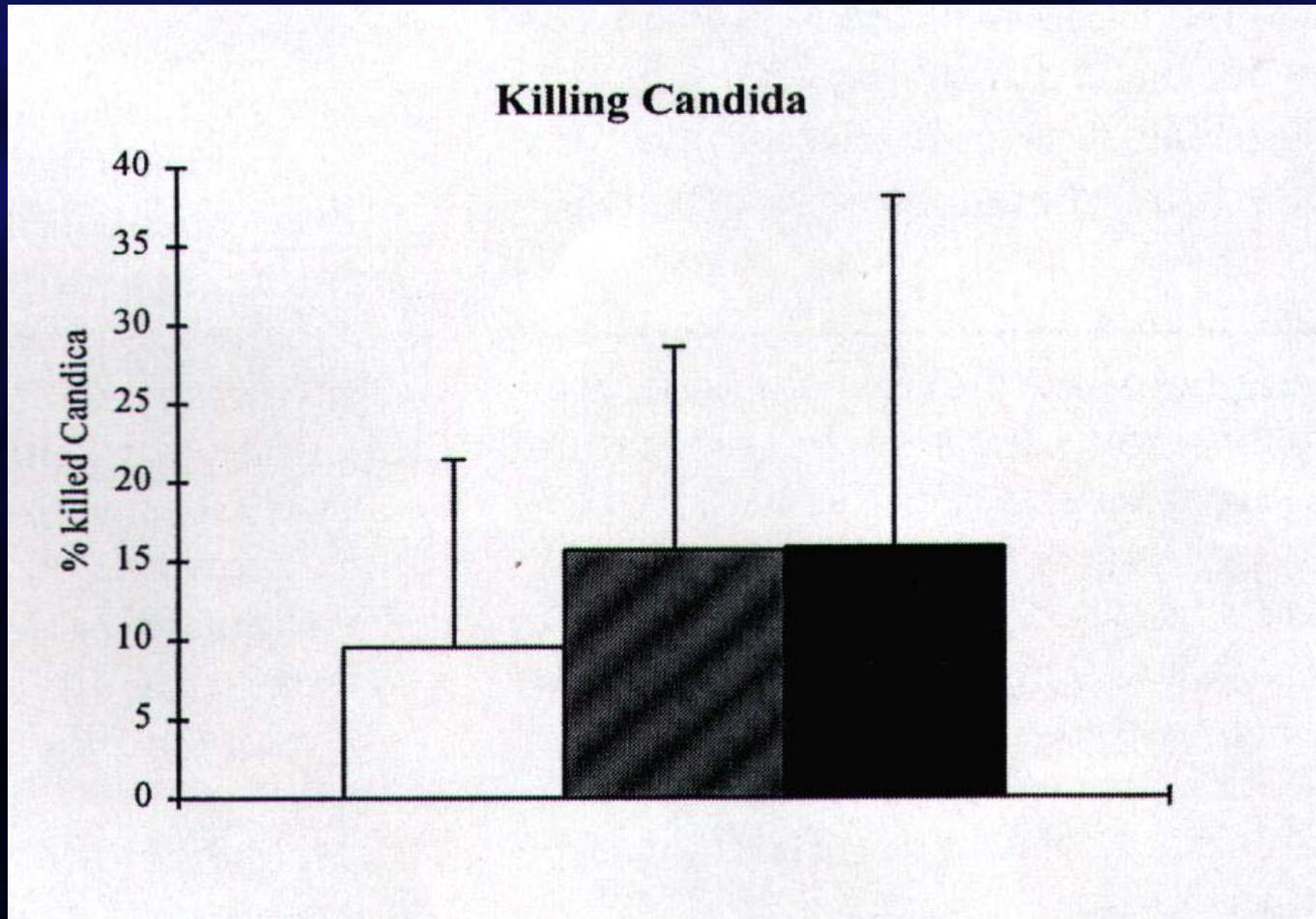
Defects in PMN function



Defects in PMN function



Defects in PMN function



BALASIOU ET AL Diabetes Care
1997;20:392-95

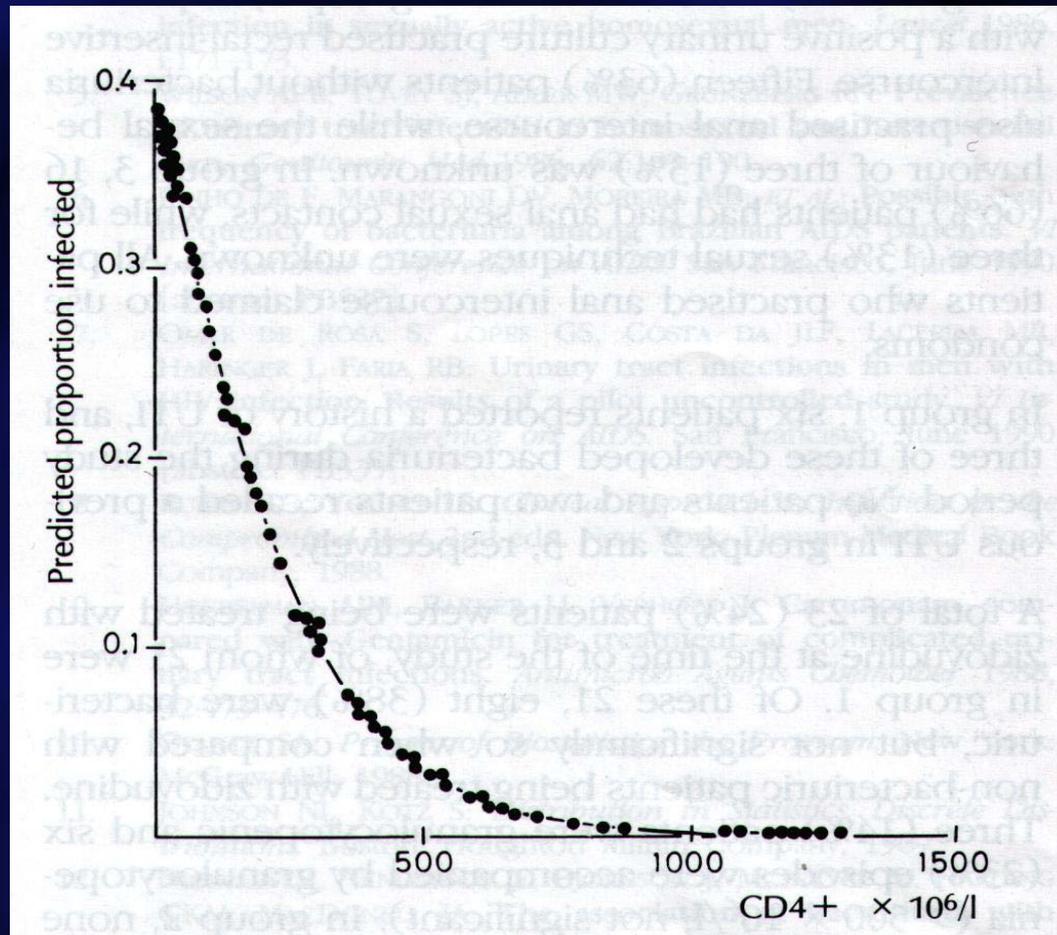
Concepts of increased rate of infection in diabetics

- Bacteria grow better in glucose
- Different micro-organisms are seen in diabetics
- Patients with diabetes mellitus are immunocompromised
 - PMN function
 - Cell mediated immunity/mucosal response

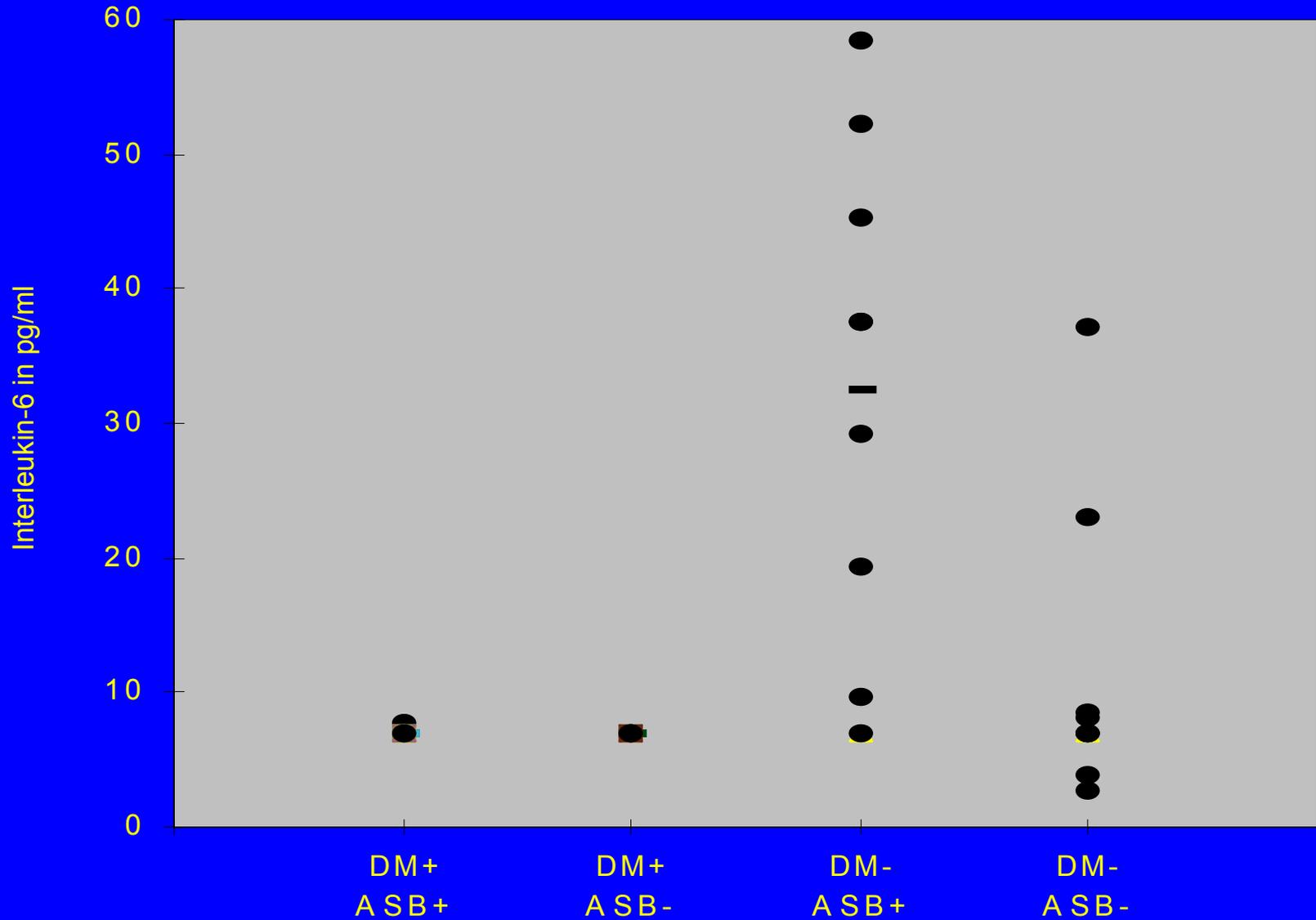
Cellular and molecular mechanisms of mucosal resistance in UTI

- C3H/HeJ mice increased susceptibility to UTI due to impaired neutrophil recruitment
- The chemokines support neutrophil migration across the uroepithelium
- IL-8R KO mice fail to clear bacteria from kidney and bladder
- Patients prone to acute pyelonefritis have a low CXC chemokine 1 expression

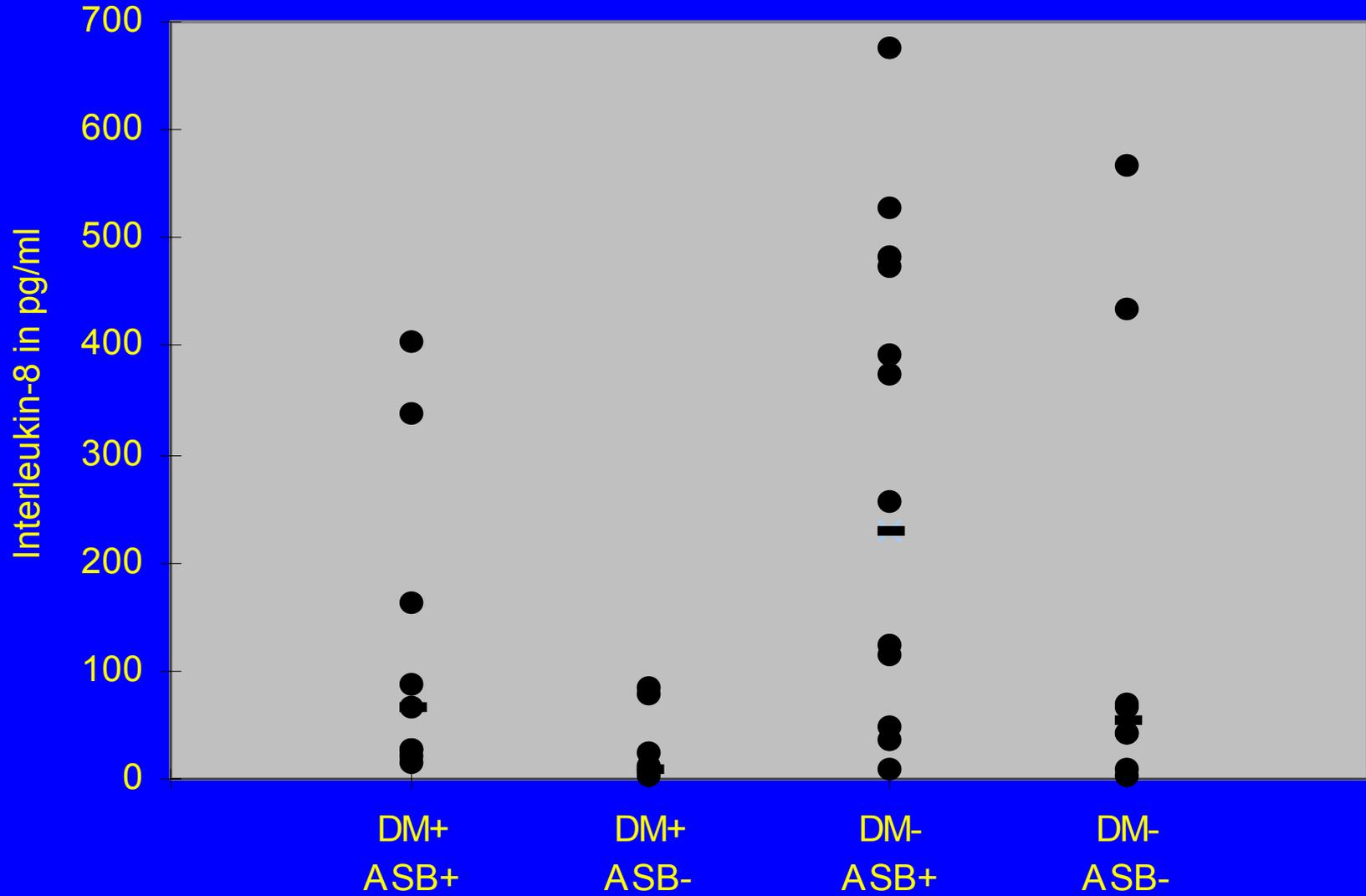
Incidence of UTI in HIV-infected man increases with decreasing CD-4 cell count



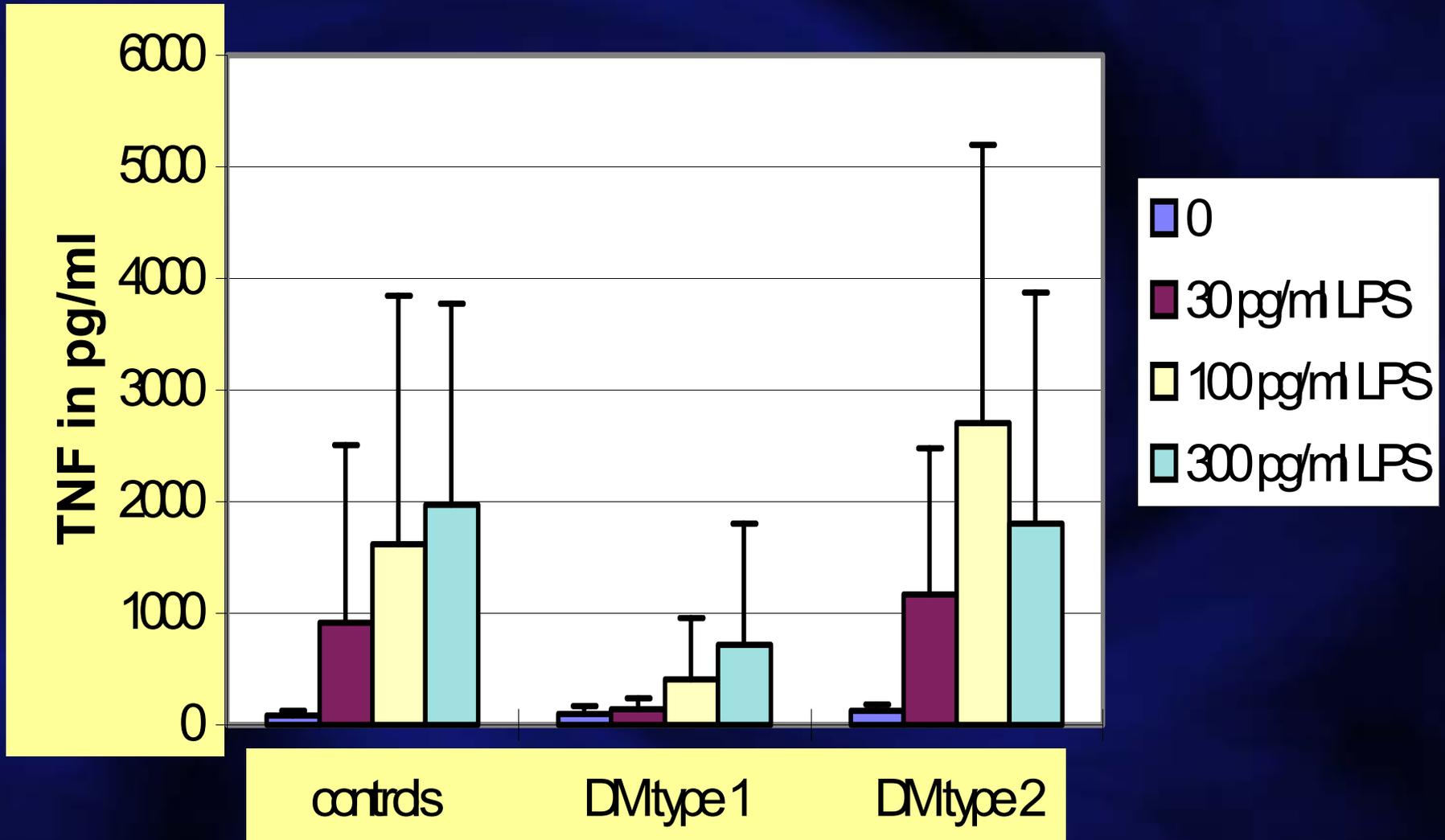
Urinary interleukin-6



Urinary interleukin-8



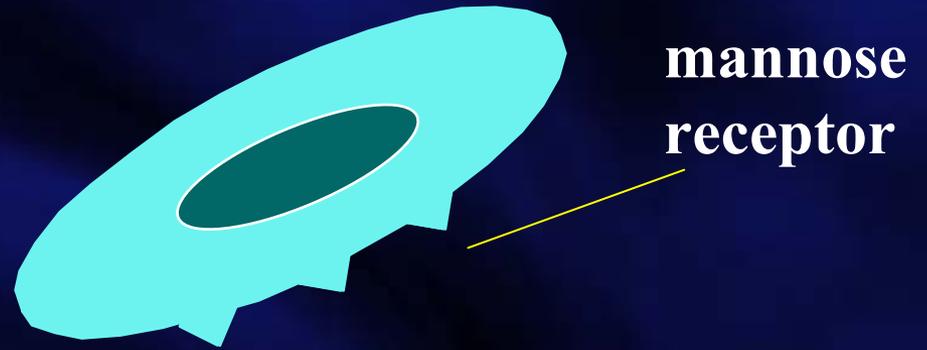
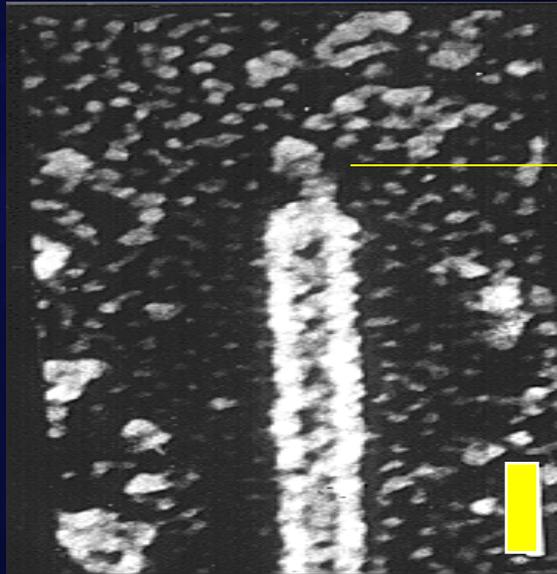
TNF (after stimulation of monocytes)



Pathogenesis of increased rate of bacteriuria in women with diabetes mellitus

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**EM
of type 1 fimbriae**



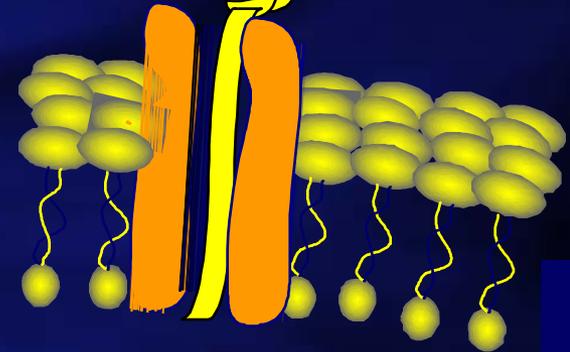
**mannose
receptor**

FimH adhesin



**type 1
pilus**

***E. coli*
outer
membrane**



FimC

(slide provided by Dr. R. Ballou)

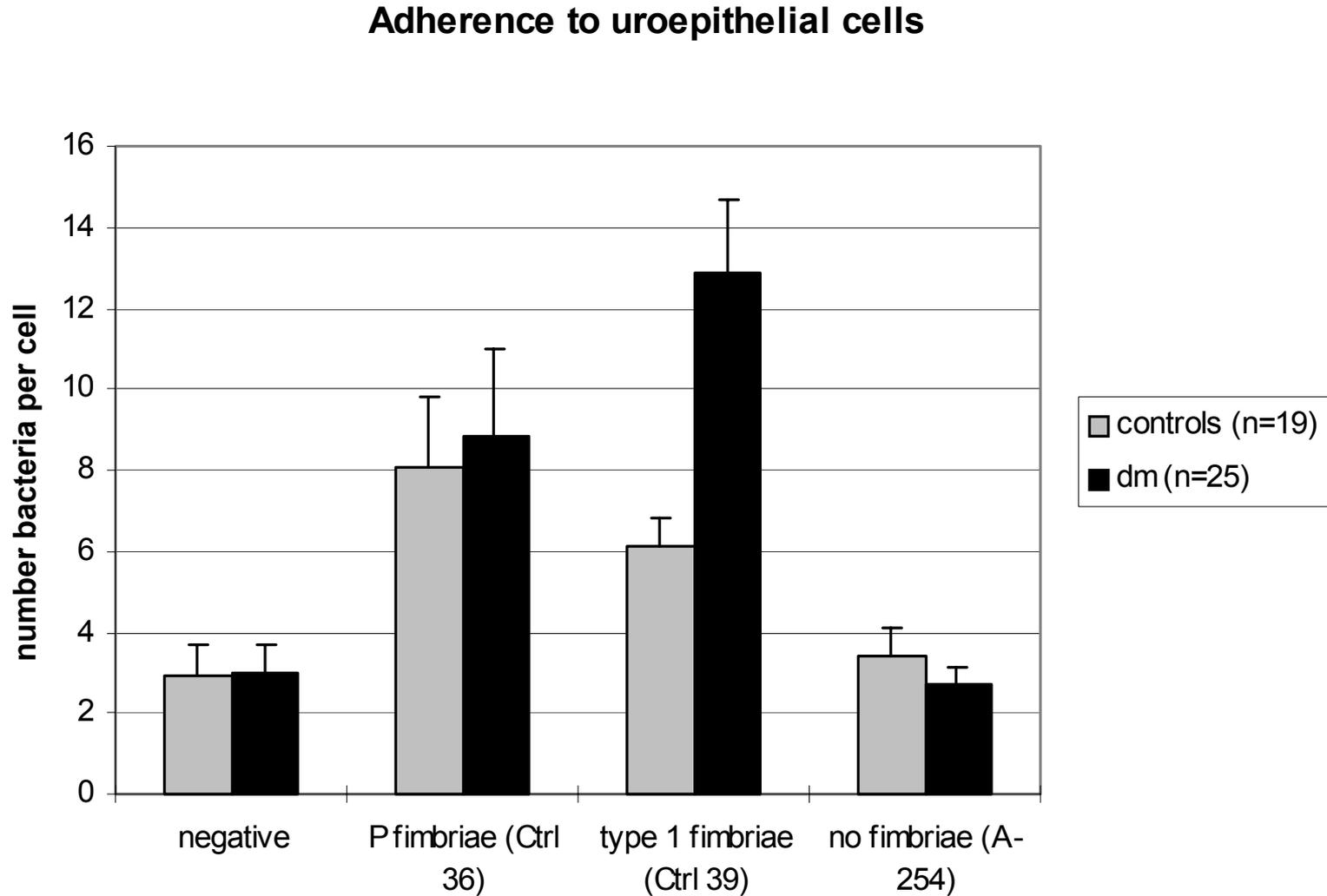
Fim H Sequence in *E.coli* from WWDM

- PCR- analysis and sequencing of our 31 *E. coli*-strains isolated from women with DM :

③ 27 identical *fimH* sequence

③ 4 were NC

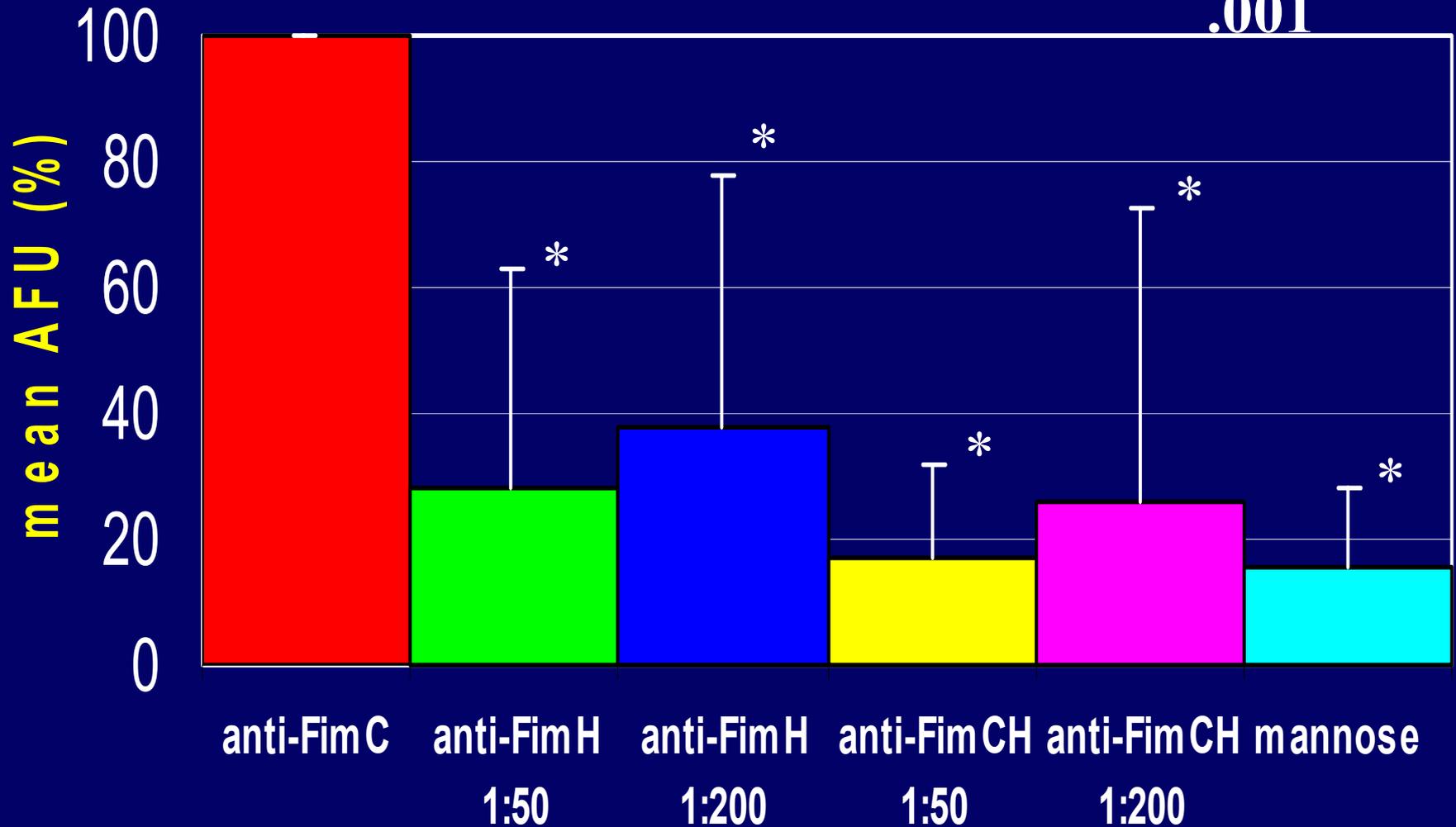
Adherence of bacteria to diabetic cells



Adherence of E.coli isolated from women with DM to T-24 cells can be inhibited

n = 14

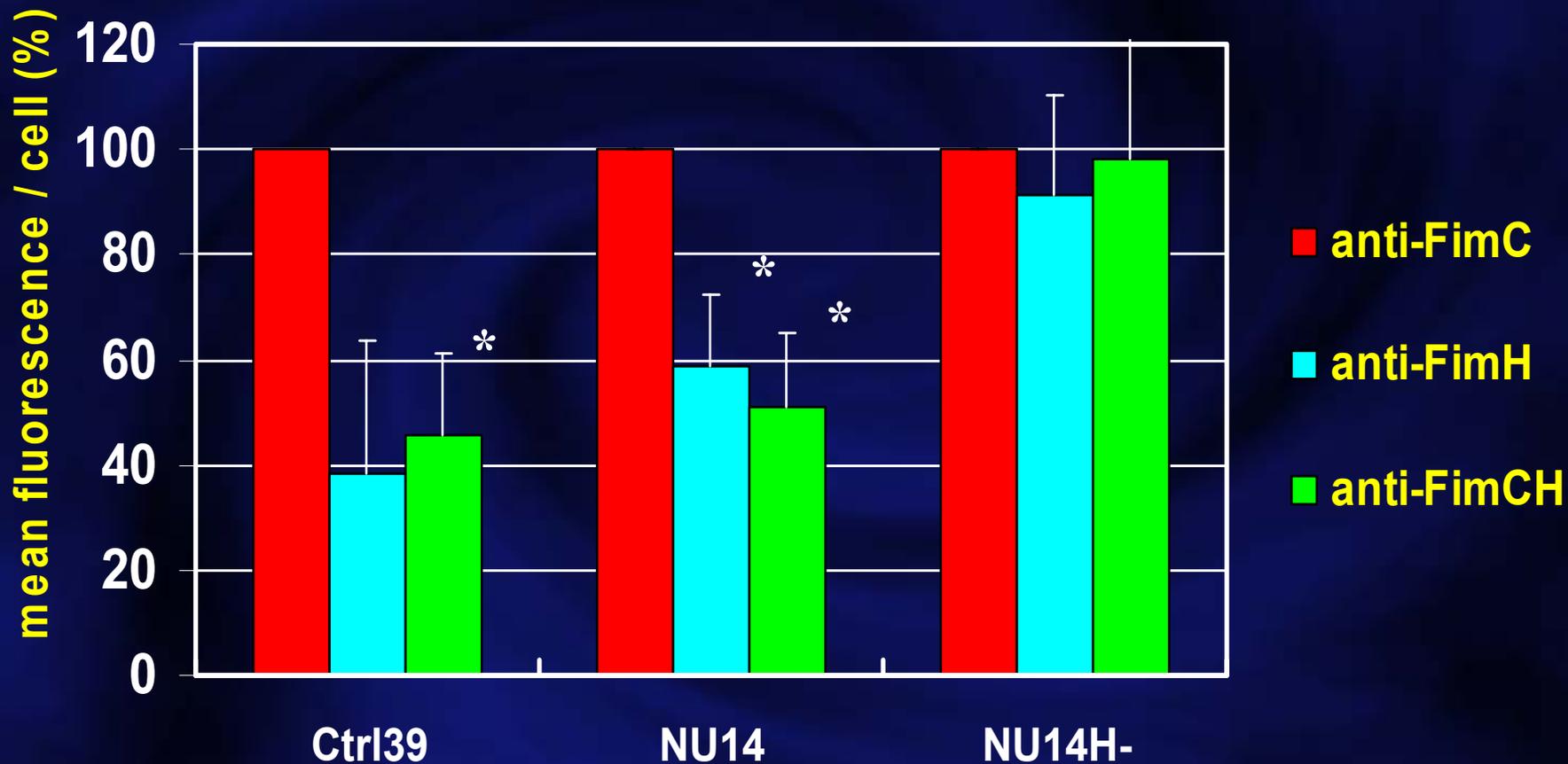
* p < .001



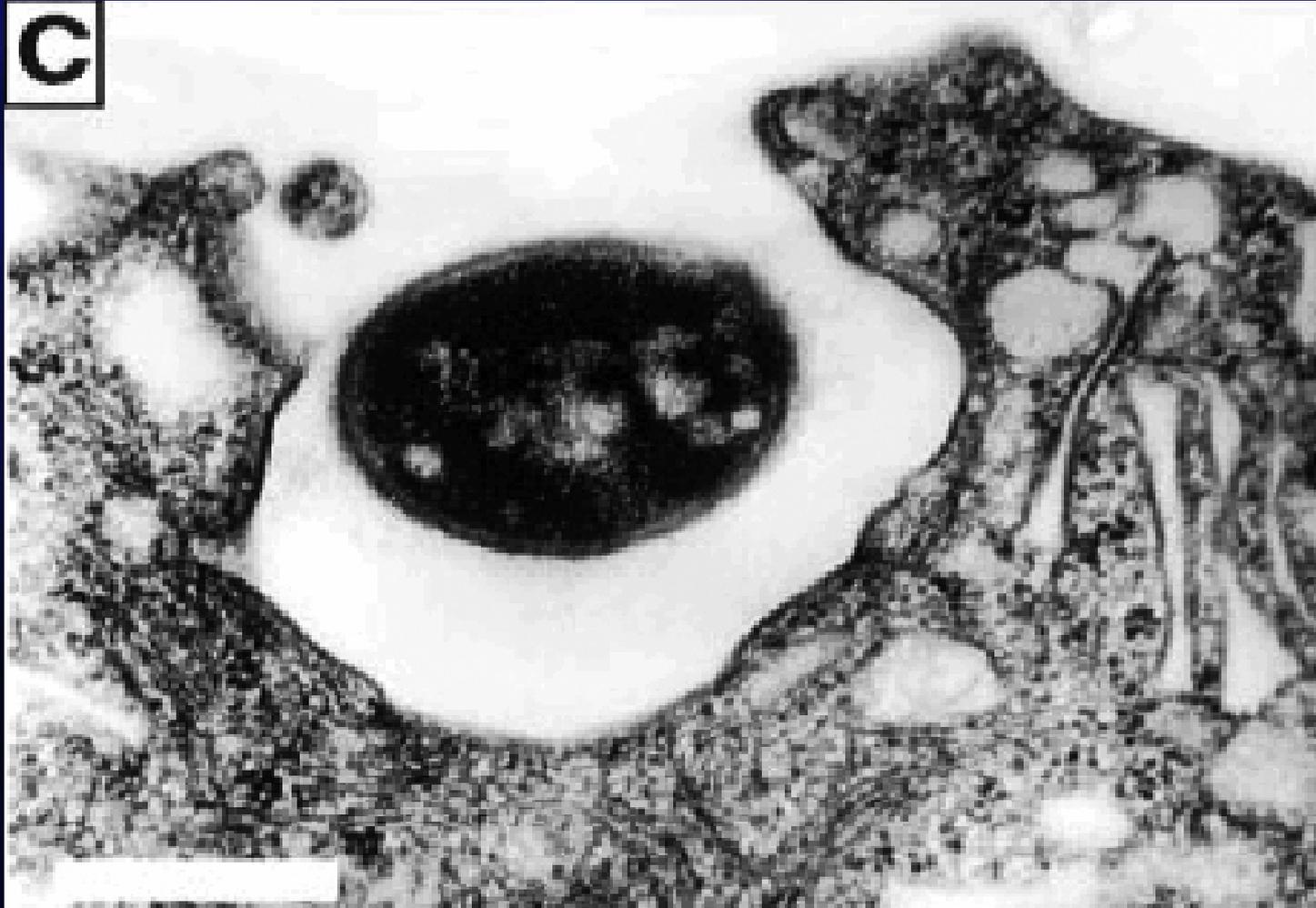
Adherence of E.coli to uroepithelial cells of women with DM can be inhibited

n = 6

* p < .05

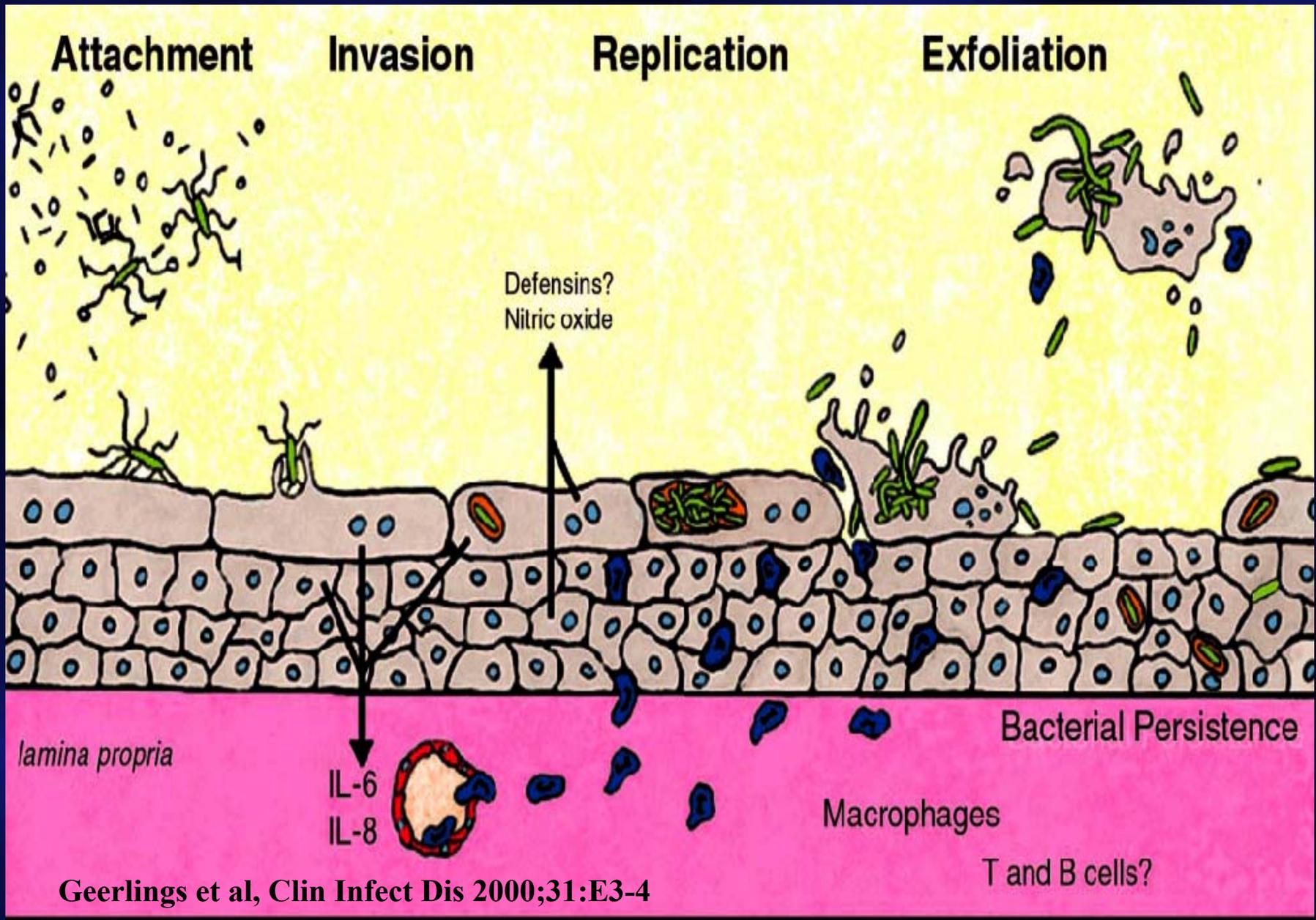


E.coli expressing type-1 pili can be internalized



Scott J Hultgren

- **FimH adhesin facilitates intimate contact with uroplakin**
- **FimH is involved in mediating internalization of UPEC**
- **Can trigger cytokine and chemokine production leading to exfoliation of uroepithelial cells**
- **Avoidance of clearance leads to a quiescent bacterial reservoir within the bladder mucosa**



Geerlings et al, Clin Infect Dis 2000;31:E3-4

\ Tamm-Horsfall protein ● uromucoid sIgA UPEC PMNs

Research goals

- **Clinical data in women with type-1 DM point out to effect of AGEs (or some other pathway) on uroepithelial cell**
- **Is adherence of E.coli also increased in animal models of DM?**
- **If so what is the mechanism?**
- **Is bacteriuria associated with renal failure?**

Acknowledgement

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Arjen Jansz

Adherence of type-1 fimbriae in WWDM

- Uroplakin is the receptor
- Protein component is the same
- Almost all strains tested have the FimH gene
- Adherence to T-24 cell of these strains can be inhibited by anti-Fim H antibodies
- Adherence of strains to uroepithelial cells of WWDM can be inhibited by anti-Fim H antibodies